



UNITED STATES PATENT AND TRADEMARK OFFICE

C/C

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

10/614,072	07/02/2003	Steven D. Goodman	89188.0046	6624
------------	------------	-------------------	------------	------

26021 7590 05/19/2005

HOGAN & HARTSON L.L.P.
500 S. GRAND AVENUE
SUITE 1900
LOS ANGELES, CA 90071-2611

EXAMINER

TONGUE, LAKIA J

ART UNIT

PAPER NUMBER

1645

DATE MAILED: 05/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/614,072

Applicant(s)

GOODMAN ET AL.

Examiner

Lakia J. Tongue

Art Unit

1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 February 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6 and 14-24 is/are pending in the application.
- 4a) Of the above claim(s) 7-13 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6 and 14-24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on February 28, 2005 is acknowledged. Claims 1-6, 14-20 and newly added claims 21-24 are pending and under consideration. Claims 7-13 have been withdrawn from consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

Objections Withdrawn

1. In view of applicant's response, the objection to the specification, page 3 paragraph 2 are withdrawn.

Rejections Withdrawn

2. In view of applicant's response, the rejection over claims 1-6 and 14-20 under 35 U.S.C. 112, page 4 paragraph 3 is withdrawn.
3. The rejection over claims 1-3 and 14-16 under 35 U.S.C 102(b) over Ooshima et al, page 5 paragraph 4 is withdrawn.

Art Unit: 1645

4. The rejection over claims 1-6 and 14-20 under 35 U.S.C 103(a) over Cvitkovitch et al in view of Kuramitsu, H. et al, page 7 paragraph 5 is withdrawn.

Rejections Maintained

5. The rejection of newly amended claims 14-17, 19 and 20 under 35 U.S.C. 102(e) is maintained for the reasons set forth in the previous Office Action page 6.

The rejection was on the ground that Cvitkovitch et al discloses an invention that relates to a compound that competitively inhibits binding of CSP to *S. mutans* histidine kinase. The invention treats or prevents dental caries by the addition of compounds that inhibit the stimulatory action of peptides on biofilm formation and acid tolerance of *S. mutans*. This is accomplished by delivery of these compounds to the biofilm and or to incorporate these inhibitors into materials to control growth on surfaces. This includes delivery by topical application, alone or in combination with other compounds including toothpaste, mouthwash, food or food additives (0028). The CSP inhibitors are useful when combined with a carrier in a pharmaceutical composition. The compositions are useful when administered in methods of medical treatments or prophylaxis of a disease, disorder or abnormal physical state caused by *S. mutans* (0078).

Cvitkovitch et al discloses compositions that can be administered to humans or animals by methods such as food, food additives, gels, toothpaste, mouthwash, dental floss or chewing gum in methods of medical treatment. Cvitkovitch et al discloses that dosages to be administered depend on individual patient condition, indication of the drug, physical and chemical stability of the drug, toxicity of the desired effect and the chosen route of administration. The compositions are used to treat disease caused by streptococcal infections such as dental caries and endocarditis (0079).

Cvitkovitch et al discloses compositions that may also contain additives such as antioxidants, buffers, bacteriostats, bactericidal antibiotics and solutes (0083). Cvitkovitch et al further discloses antibodies directed against the CSP would provide protection against caries (0085). The CSP peptide is also useful as an antigen for the preparation of antibodies that can be used to purify or detect other CSP-like peptides (0093).

Applicant urges that a) Cvitkovitch et al fails to teach a medicament comprising CSP for the treatment or prophylaxis for reducing the attachment of *S. mutans* to teeth,

b) Cvitkovitch et al teaches competitive inhibitors of CSP and not CSP itself, c)
Cvitkovitch et al has no teaching or suggestion of a medicament comprising CSP and d)
Cvitkovitch et al achieves a completely different result than that of the present invention.

It is the examiner's position that the claims are drawn to a medicament for the treatment or prophylaxis of a condition associated with the attachment of *S. mutans* to teeth, comprising CSP in an amount effective to reduce the attachment of *S. mutans* to teeth. The medicament comprises at least one substance selected from a group consisting of sucrose, an orally acceptable carrier, an anti-caries agent and mixtures thereof. Figure 5 and SEQ ID NO: 2 is identical to SEQ ID NO: 1 of the instant application. Cvitkovitch et al discloses a vaccine where the CSP provides protection against caries (0085). The vaccine is viewed as intended use. Cvitkovitch et al disclose CSP in toothpaste, mouthwashes or chewing gum (0084). Inherently the toothpaste, mouthwashes or chewing gum (medicament) would have the capability of preventing attachment of *S. mutans* to teeth.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-6 and 14-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising an isolated Competence Stimulating Peptide (CSP) and sucrose, wherein the CSP comprises SEQ ID NO: 1, does not reasonably provide enablement for a modification thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification is enabling only for a composition comprising an isolated Competence Stimulating Peptide (CSP) and sucrose, wherein the CSP comprises SEQ ID NO: 1. The specification states: "It is to be understood all peptides and proteins having the same or similar function as the CSP peptide encoded by the sequence shown in Figure I (SEQ ID NO: 1) are considered to be functional equivalents of this peptide and are also included within the scope of this invention. Accordingly, the terms "S. mutans CSP" and "CSP" as used herein encompass S. mutans and all functional equivalents thereof. (p6, lines 17-21).

There is no guidance provided as to which amino acids can be deleted and the polypeptide would retain its biological function. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence

Art Unit: 1645

and still retain similar activity requires a knowledge with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the polypeptide's structure relates to function. However, the problem of the prediction of polypeptide structure from mere sequence data of a single polypeptide and in turn utilizing predicted structural determinations to ascertain functional aspects of the polypeptide and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation. There is no guidance as to what amino acids may be changed, wherein the CSP is still capable of preventing attachment of *S. mutans* to teeth. The claims broadly teach a modification thereof, which include substitutions and/or deletions, therefore any polypeptide is being claimed, and no specific location for the deletion, and substitution or any combination thereof is recited. Thus, the resulting polypeptide could result in a polypeptide not taught nor enabled by the specification.

Thomas E. Creighton, in his book, "Proteins: Structures and Molecular Properties, 1984", (pages 314-315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause mutant hemoglobin to have lower stabilities due to any of several causes: 1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge; 2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a Proline residue, which must distort

Art Unit: 1645

the alpha-helix; 3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book "Protein Structure: A Practical Approach, 1989; pages 184-186" teaches that present day site directed mutagenesis of a gene allows any amino acids in a protein sequence to be changed to any other, as well as introducing deletions and insertions". The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in "Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph) adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

There is no guidance provided in the specification as to how one would begin to choose "a CSP with modification thereof". The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does not disclose the following:

- the general tolerance to modification and extent of such tolerance;
- specific positions and regions of sequence(s) which can be predictably modified and which regions are critical;
- what modifications can be made which would retain the biological activity of the intact protein; and

Art Unit: 1645

- the specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

The state of the art with respect to a modification of a sequence has been burdensome. Kumar, V. et al (Amino acid variations at a single residue in an autoimmune peptide profoundly affect its properties: T-cells activation, major histocompatibility complex binding, and ability to block experimental allergic encephalomyelitis, Immunology, 1990; 87: 1337-1341) "shows that most substitutions in at position 4 in the N-terminal encephalitogenic MBP peptide can dramatically alter the ability of variant peptides to activate T cells and to bind to the I-A molecule.....substitutions appear to increase the ability of the peptide to bind to the MHC molecule, others fail to generate an effective immune response *in vivo* (page 1340)".

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to the modification of sequences having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make and use polypeptides that are fragments or epitopes of CSP in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the protein's structure and still maintain activity is unpredictable and the experimentation left those skilled in the art is unnecessarily and improperly, extensive and undue. See *Amgen Inc v Chugai Pharmaceutical Co Ltd*. 927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and *Exparte Forman*, 230 U.S. P.Q. 546(Bd. Pat. App & int. 1986).

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1-6 and 14-24 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Cvitkovitch et al (U.S. Patent Application Publication U.S. 2002/0081302 A1).

Claims 1-6 and 14-24 are drawn to a composition comprising an isolated Competence Stimulating Peptide (CSP) and sucrose, wherein the CSP comprises SEQ ID NO: 1, or a modification thereof, wherein the CSP is capable of preventing the attachment of *S. mutans* to teeth.

Cvitkovitch et al discloses an invention that relates to a compound that competitively inhibits binding of CSP to *S. mutans* histidine kinase. The invention treats or prevents dental caries by the addition of compounds that inhibit the stimulatory action of peptides on biofilm formation and acid tolerance of *S. mutans*. This is accomplished by delivery of these compounds to the biofilm and or to incorporate these inhibitors into materials to control growth on surfaces. This includes delivery by topical application, alone or in combination with other compounds including toothpaste, mouthwash, food or food additives (0028). The CSP inhibitors are useful when combined with a carrier in a pharmaceutical composition. The compositions are useful when administered in methods of medical treatments or prophylaxis of a disease, disorder or abnormal physical state caused by *S. mutans* (0078). Inherently the claimed composition would have sucrose in the toothpaste.

Cvitkovitch et al discloses compositions that can be administered to humans or animals by methods such as food, food additives, gels, toothpaste, mouthwash, dental floss or chewing gum in methods of medical treatment. Cvitkovitch et al discloses that dosages to be administered depend on individual patient condition, indication of the drug, physical and chemical stability of the drug, toxicity of the desired effect and the chosen route of administration. The compositions are used to treat disease caused by streptococcal infections such as dental caries and endocarditis (0079).

Cvitkovitch et al discloses compositions that may also contain additives such as antioxidants, buffers, bacteriostats, bactericidal antibiotics and solutes (0083).

Art Unit: 1645

Cvitkovitch et al further discloses antibodies directed against the CSP would provide protection against caries (0085). The CSP peptide is also useful as an antigen for the preparation of antibodies that can be used to purify or detect other CSP-like peptides (0093).

In the alternative the specification does not specifically teach an amount of CSP in a composition or a medicament. A limitation such as an amount of CSP to be present in a composition or medicament is being viewed as limitations of optimizing experimental parameters.

Since the Office does not have the facilities for examining and comparing applicants' composition with the composition of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

Art Unit: 1645

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakia J. Tongue whose telephone number is 571-272-2921. The examiner can normally be reached on Monday-Friday 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

LST
LJT


LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600